Long-term outcomes of second-line vs later-line zanubrutinib treatment in patients with relapsed/refractory MCL: an updated pooled analysis

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Introduction: Zanubrutinib as an effective treatment option for mantle cell lymphoma (MCL) has been approved in the United States and China as monotherapy in patients with relapsed/refractory (R/R) MCL. We previously reported results of a pooled analysis of two zanubrutinib studies (BGB-3111-206 and BGB-3111-AU-003) with a median follow-up of 24.9 months, and showed numerically better progression free survival (PFS) and overall survival (OS) when zanubrutinib was administered in the second line compared with administered in later lines for R/R MCL. Here, we present a longer follow-up (median 35.2 months) of the pooled data sets to compare long-term outcomes of second-line (with 1 prior line of therapy) vs later-line (with >1 prior lines of therapy) zanubrutinib treatment for R/R MCL patients.

Methods: Patient-level data were pooled for R/R MCL patients treated with zanubrutinib from a phase I study (BGB-3111-AU-003, NCT02343120) and a phase II study (BGB-3111-206, NCT03206970). The patients were divided into two groups based on the line of zanubrutinib: the second-line and the later-line group. Inverse propensity score weighting method was used to balance the baseline covariates between the groups to mimic a randomized controlled trial. The primary outcome measure was OS. Secondary outcomes included PFS, PFS rate and OS rate at 12, 24 and 36 months, objective response rate (ORR) and duration of response (DOR). Survival probability was estimated by the Kaplan–Meier method. Cox proportional hazards model was used to compute hazard ratio (HR) and 95% confidence interval (CI) for PFS and OS. P value of less than 0.05 was considered to indicate statistical significance. However, hypothesis testing was not pre-stated. The safety profile in each arm was summarized.

Results: Among the 112 (79 in BGB-3111-206, 33 in BGB-3111-AU-003) patients with R/R MCL pooled, 41 (36.6%) received zanubrutinib as second-line therapy; 71 (63.4%) patients received as later-line. The median follow-up time for the second-line and the later-line group was 36.07 and 34.37 months, respectively. After weighting, all baseline covariates were balanced, and the prevalence of prior medication use in each group were preserved. OS was statistically significantly longer in the second-line group vs the later-line group (HR 0.459 [95% CI, 0.215-0.980], $p = 0.044$), with the median OS not reached in both groups (Figure). The median PFS was similar but numerically longer in the second-line group (27.8 months, 95% CI, 16.76-NE) vs the later-line group (22.1 months, 95% CI 16.62-45.50) (HR 0.78 [95%

CI, 0.443-1.373], p = 0.389). Efficacy outcomes in each group are summarized in the Table below. The safety profile was similar between the two groups; zanubrutinib was generally well tolerated and there were no new safety concerns during the long-term follow-up.

Conclusion: The long-term follow-up further confirmed that second-line zanubrutinib treatment was significantly associated with prolonged OS compared with later-line treatment in patients with R/R MCL.

Figure. OS after weighting

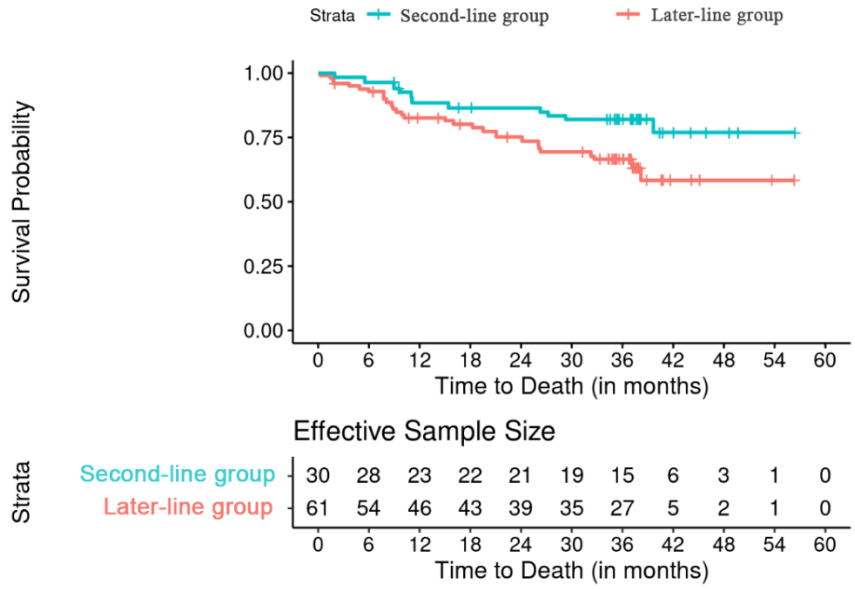

Table. Summary of efficacy outcomes before and after weighting

	Before weighting		**After weighting**	
	Second-line group (n=41)	**Later-line group (n=71)**	**Second-line group (EES=30)**	**Later-line group (EES=61)**
ORR, % (95% CI)	87.8 (0.737, 0.959)	83.1 (0.723, 0.91)	88.6 (0.738, 0.966)	85.7 (0.756, 0.928)
Median DOR, months (95% CI)	NR (14.72, NE)	30.6 (19.52, 43.07)	25.2 (14.06, NE)	25.1 (17.48, 43.01)
Median PFS, months (95% CI)	27.8 (16.76, NE)	25.8 (16.69, 45.50)	27.8 (16.76, NE)	22.1（16.62, 45.50)
Median OS, months (95% CI)	NR (NE, NE)	NR (37.13, NE)	NR (NE, NE)	NR (38.18, NE)
PFS rate at, % (95% CI)				
12 months	77.3 (0.658, 0.915)	69.6 (0.598, 0.814)	81.6 (0.707, 0.945)	68.0 (0.572, 0.817)
24 months	53.3 (0.405, 0.719)	50.3 (0.401, 0.639)	52.4 (0.387, 0.743)	49.8 (0.391, 0.645)
36 months	45.3 (0.329, 0.644)	36.8 (0.268, 0.520)	44.8 (0.318, 0.669)	35.4 (0.250, 0.523)
OS rate at, % (95% CI)				
12 months	84.9 (0.748, 0.967)	79.9 (0.712, 0.899)	88.4 (0.798, 0.982)	82.6 (0.742, 0.921)
24 months	82.3 (0.717, 0.951)	72.1 (0.625, 0.837)	86.4 (0.772, 0.970)	75.2 (0.657, 0.866)
36 months	74.1 (0.620, 0.893)	62.4 (0.521, 0.755)	82.0 (0.717, 0.941)	66.5 (0.560, 0.795)

Abbreviations: ORR, objective response rate; DOR, duration of response; PFS, progression free survival; OS, overall survival; CI, confidence interval; NR, not reached; NE, not estimable; EES, effective sample sizes.